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Proteinuria in IgA nephropathy

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Proteinuria in IgA nephropathy. Clinicopathological data in 74 patients with IgA nephropathy were analyzed with special attention to level of proteinuria and its prognostic significance in this disease. Excretion rates exceeding 3 g per day (heavy), in the range of 1 to 2.9 g (moderate) and under 1 g per day (mild) each occurred in approximately equal proportions of patients. One-sixth of those with more than 1 g developed end-stage renal failure, while serum creatinine never exceeded 2 mg/dl in any with mild proteinuria. "Renal survival" (serum creatinine of 2 mg/dl or less) at five years after presentation was 100% in patients with persistently mild proteinuria, 87% in those whose protein excretion reached the moderate range, and 69% when heavy or nephrotic range proteinuria developed. Of significance, only rarely did mild proteinuria at presentation increase to higher levels. A correlation existed between level of protein excretion and severity of mesangial, segmental or global proliferation, glomerulosclerosis, podocyte effacement, interstitial infiltration, tubular atrophy and vascular sclerosis, even in patients with unimpaired renal function. Moderate or heavy proteinuria typically preceded the onset of hypertension and occurred prior to the development of renal insufficiency. Our results underscore magnitude of proteinuria as an early marker of glomerular damage in the prognosis of IgA nephropathy.

Since the first description of mesangial IgA nephropathy [1], the disease has been observed world wide. The primary form of IgA nephropathy (Berger's disease) is defined immunopathologically by predominant mesangial deposition of IgA, accompanied by C3 or other immunoglobulins. The spectrum of histological abnormalities includes a full range of glomerular changes from normal or minimal to various combinations of proliferation in the mesangium and peripheral capillary loops, tuft necrosis and small or circumferential crescents. Clinically IgA nephropathy is a chronic disease characterized by microhematuria with or without episodes of gross hematuria, often with minimal proteinuria.

IgA nephropathy was originally considered a benign disease with favorable prognosis [1]. Subsequently, its frequently progressive nature has been noted [2–7], and it has been estimated that this form of glomerular disease may account for as much as 10% of all end-stage renal failure cases [8]. As with other intrinsic renal diseases, once hypertension and renal functional impairment develop, eventual progression to uremia is inevitable. Similarly, the histological findings of glomerular sclerosis, vascular sclerosis and interstitial fibrosis carry the anticipated poor prognosis associated with irreversible parenchymal damage [9–13]. Obviously it would be helpful to identify early clinical or histological features which bear prognostic significance.

In the present study we have examined the correlations between extent of proteinuria and the clinical course of IgA nephropathy. The findings clearly demonstrate a benign outcome with minimal proteinuria and an unfavorable prognosis with moderate or heavy proteinuria.

Methods

Clinical and pathological data of all patients with the diagnosis of IgA nephropathy at NYU Medical Center from July 1970 through December 1983 were reviewed. The diagnosis was made if immunofluorescence revealed the predominance of immunoglobulin A deposits in glomeruli in the absence of lupus erythematosus, cirrhosis of the liver and Henoch-Schönlein purpura. Out of 78 patients who satisfied these criteria, 74 with sufficient data on their level of proteinuria form the basis of this study. Proteinuria was said to be mild if 24-hour urine protein excretion was less than 1 g, moderate if it was between 1 and 2.9 g and heavy if in the nephrotic range, that is, 3 g or more. Twenty-four-hour urinary protein determinations were performed as clinically indicated. All except six patients with mild proteinuria had one or more quantitative determination. These six had multiple qualitative urinalyses showing negative to trace amounts of protein excretion. Three or more quantitative determinations, ranging up to 35 per patient, were available in 24% of those with mild proteinuria, 45% with moderate proteinuria and 60% with heavy proteinuria. Greater than 2 red cells per high power field was interpreted as microscopic hematuria. Hypertension was defined as a systolic blood pressure of 160 mm Hg or greater, or a diastolic exceeding 90 mm Hg.

Renal biopsies were fixed in Zenkers FU48, cut at 2 to 3 microns and stained with hematoxylin eosin, periodic acid silvermethenamine counterstained with hematoxylin and eosin, and in some cases with periodic acid Schiff and azacarmine. Tissue for immunofluorescence was frozen in a cryostat, sectioned at 4 microns and reacted with fluorescein-labelled antisera against IgG, IgA, IgM (heavy chain specific), C3 and fibrinogen-fibrin. Some biopsies were also stained with fluorescein-labelled antisera each monospecific against kappa or lambda light chain, C4 and Clq. For electron microscopy, material was fixed in 2.5% buffered gluteraldehyde, post-fixed in osmium tetroxide and embedded in epon. Thin sections double-stained with uranyl acetate and lead citrate were exam-

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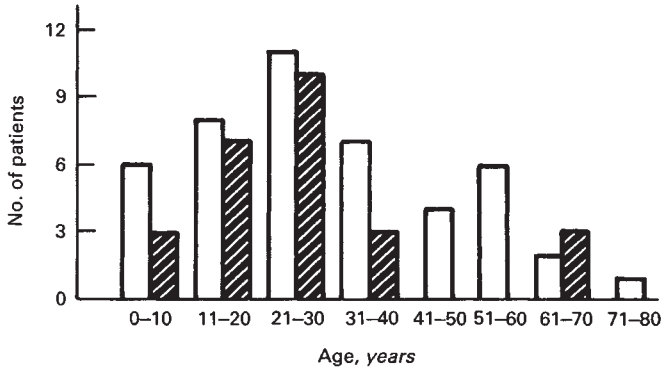

Fig. 1. *Sex and age at presentation of IgA nephropathy.* Males predominate. Peak age for presentation is third decade. Symbols are: (□) male; (▨) female.

ined and photographed in a Zeiss EM9 or EM10A electron microscope.

Biopsies that contained at least 7 glomeruli were included for analysis. Chi-square contingency table analysis was used to test the frequency distribution of single clinical and immunopathologic features in the three groups representing increasing levels of proteinuria. In each biopsy the severity of mesangial proliferation, interstitial infiltration and tubular atrophy was semiquantitatively graded from 0 to 2+, and vascular sclerosis from 0 to 3+. Electron microscopic findings of increase in mesangial matrix and podocyte effacement were graded 0 to 2+ and mesangial deposits 0 to 3+. The median ranks of the three groups with increasing levels of proteinuria were compared using Wilcoxon test between two groups and Kruskal-Wallis test for ordered classification among three groups.

Life table analysis of patients according to gender, age distribution and different levels of proteinuria was performed by the method of Cutler and Ederer [14] and compared using the log rank test. A P value of less than 0.05 was considered significant. For life table analysis, we selected as end-point a serum creatinine concentration exceeding 2 mg/dl, as indicative of unequivocal impairment of renal function. In a slowly progressive disease such as IgA nephropathy, the use of end-stage renal failure as end-point makes identification of a prognostic feature much more difficult and would over-estimate the number with a favorable prognosis.

Results

Mode of presentation

Presentation was most common in the second and third decades (51% of all cases; Fig. 1). Forty-seven patients were male and 27 female. Thirty-six were caucasian, 23 hispanic, 8 oriental, 4 black and 3 of other ethnic groups. Rarity of this disease in blacks has been observed by others [15, 16]. Blacks accounted for 5.4% of patients with IgA nephropathy in our series whereas the proportion of blacks treated in our medical center is 37.5%. Thirty-four patients (46%) presented with gross hematuria, 34 with an abnormal urinalysis on routine examination, 5 with edema and 1 with uremia.

An "acute nephritic" onset, defined as fluid retention with transient hypertension, occurred in 5 patients, 3 of whom had gross hematuria, 4 edema and 2 circulatory congestion. Hypertension subsided within 2 months in all 5 patients, and renal function remained normal on subsequent follow-up.

Gross hematuria

In addition to 34 patients who presented with gross hematuria, 6 others developed it subsequently, a total of 40 in all. Gross hematuria occurred repeatedly in 31. In 23 of the 40 patients it was associated with an upper respiratory illness, or in some cases abdominal symptoms.

Microscopic hematuria

Microscopic hematuria was commonly present between episodes of gross hematuria. Of the 34 patients without gross hematuria, microscopic hematuria was observed in all but 3.

Proteinuria

Proteinuria was present in all but four patients, but in only one of these four was its absence documented on more than one occasion. Maximum level of 24-hour protein excretion during the period of observation reached 3 g or more in 25 (Group III), 1 to 2.9 g in 20 (Group II) and was less than 1 g in 29 patients (Group I). Of the 25 patients in Group III, 13 demonstrated heavy proteinuria at the time of presentation and 12 developed it 6 months to 10 years later. Among these 12, proteinuria had been in the moderate range (1.0 to 2.9 g) in five individuals and in the mild range (less than 1 g) in two prior to becoming heavy. Such information was not available in the remaining five patients. Of the 13 with early heavy proteinuria, it declined in five after three months to a year; three of these five had an "acute nephritic" presentation. Heavy proteinuria proved to be persistent in the remaining eight who demonstrated this feature at presentation, and in all 12 who developed it later. As will be seen, persistent heavy proteinuria was associated with a poor prognosis.

Hypertension

Hypertension was observed in a total of 27 patients (36.5%). Eighteen were hypertensive on presentation; in five of these, hypertension was considered an "acute nephritic" manifestation since it proved to be transient (see above). Of the 22 patients with persistent hypertension, 14 had a serum creatinine concentration of less than 2 mg/dl at onset of hypertension. Ten of these 14 were available for follow up; in five, renal function remained stable over a period of 1 to 8-1/2 years, while in the others it deteriorated over 1 to 10 years to end-stage renal disease in three (all with heavy proteinuria), and in two to serum creatinine concentrations of 2 and 2.1 mg/dl. Eight of the 22 patients with persistent hypertension had serum creatinines ranging from 2 to 5.8 mg/dl when hypertension was first detected. Follow up was available in seven of these; three reached end-stage renal failure and three showed deterioration of renal function with creatinine concentrations of 4.4, 7.5, and 8.5 mg/dl at latest observation. The other patient had a stable creatinine of 2 mg/dl over a two year period. In 13 of 22 patients (59%) with persistent hypertension serum creatinine concentrations of 2 mg/dl or greater developed, while 15 of 21 (71%) with serum creatinines of 2 mg/dl or more were hypertensive,

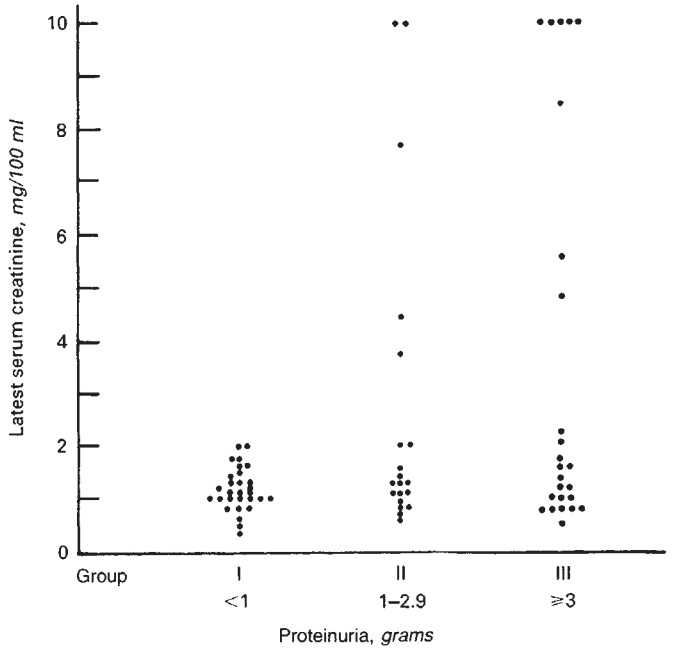

Fig. 2. *Latest serum creatinine according to level of proteinuria in IgA nephropathy.* Fifteen patients in whom proteinuria exceeded 1 g. reached serum creatinines in excess of 2 mg/dl, 7 of whom developed end-stage renal failure. Serum creatinine never exceeded 2 mg/dl in those with less than 1 g of proteinuria, even though mean follow up period was the longest in this group.

indicating the frequent association of hypertension with renal functional impairment in this disease. In 20 of 22 patients (90%) moderate to heavy proteinuria antedated hypertension, demonstrating the rarity of hypertension in patients with mild proteinuria and underlining extent of proteinuria as an earlier prognostic feature than hypertension.

Renal function

At the time of latest observation, seven patients (9.5%) had developed end-stage renal failure (Fig. 2). Of these, one presented with uremia, while the others developed it 1, 3, 5-3/4, 8, and 13 years after presentation. Eight additional patients progressed to renal insufficiency (serum creatinines ranging from 2.1 to 8.5 mg/dl). The relative risk of renal insufficiency (serum creatinine exceeding 2 mg/dl) was 12.88 times greater in patients who were 30 years and older than that for patients under 30 years ($P < 0.001$), and 1.85 times greater in males than in females (NS). The rate of decline in renal function varied widely. At latest observation, 59 patients had serum creatinines of 2 mg/dl or less.

Correlations with proteinuria

Mean age at presentation of renal disease was 22 ± 15.9, 33 ± 20.9 and 34 ± 17.4 years in Groups I, II and III, respectively (NS). There was an increase in male preponderance with increasing concentrations of proteinuria, with male to female ratios of 1:4, 1:9 and 2:1 in the groups (NS). Recurrent gross hematuria occurred most often in Group I, 55%, compared to 30% and 36% in Groups II and III (NS). Patients with recurrent gross hematuria (51.6%) had mild proteinuria compared to 35% in the others. Persistent hypertension developed in 48% of Group III, 40% of Group II and 7% of Group I (P for Group I vs. Group II <0.05, Group I vs. Group III <0.01 and Group II vs. Group III NS). Moderate to heavy proteinuria preceded development of hypertension in the vast majority of patients. Twenty of 22 patients with persistent hypertension (90%) already had moderate to heavy proteinuria at the time of discovery of hypertension. Significantly, 24 of 34 patients (70%) with moderate and heavy proteinuria at presentation were not yet hypertensive. Seven out of 12 patients with heavy proteinuria and persistent hypertension developed either end stage renal failure or advanced renal insufficiency.

Proteinuria and development of renal functional impairment. The latest serum creatinine concentrations in patients who developed the different levels of maximal proteinuria are shown in Figure 2. Forty per cent of Group III and 25% of Group II developed serum creatinines exceeding 2 mg/dl at the end of a mean follow-up period of 34 months and 61 months, respectively, whereas no patient in Group I reached a serum creatinine exceeding 2 mg/dl after a mean follow-up of 84 months. Five in Group II and eight in Group III reached serum creatinines exceeding 3 mg/dl; two in the former and five in the latter progressed to end-stage renal failure.

Utilizing a serum creatinine concentration in excess of 2 mg/dl as the end point, life table analysis was performed according to the method of Cutler and Ederer [14]. Figure 3 shows "renal survival" according to maximal level of proteinuria which was attained during their course in 67 patients with serum creatinine of 2 mg/dl or less at presentation. Group III patients were more likely to experience renal functional impairment than those in Group I ($P < 0.001$). "Renal survival" in Group II was intermediate between these two extremes. "Renal survival" at five years after presentation of renal disease was 100% in Group I, 87% in Group II and 69% in Group III. Five years from the first appearance of heavy proteinuria "renal survival" proved to be only 55%.

The prognostic significance of level of proteinuria at presentation of IgA nephropathy is plotted in Figure 4. Thirty-three patients with mild proteinuria, 18 with moderate proteinuria and 13 with heavy proteinuria at presentation who had serum creatinine of 2 mg/dl or less were the subjects of this analysis. Again, a serum creatinine concentration exceeding 2 mg/dl was taken as the end point for "renal survival". Using a log rank test for trend as described by Peto et al [17], the relative risk of ultimate renal functional impairment in patients with moderate proteinuria on presentation was 2.5 times greater, and with heavy proteinuria 6.3 times greater than those with mild proteinuria ($P < 0.05$). Four patients out of 33 with mild proteinuria at presentation later developed greater proteinuria, two in the moderate and two in the heavy range. These increases in proteinuria occurred within one year after presentation except for one patient who developed nephrotic levels and a rapid decline in renal function after three years. Thus, the data demonstrate not only a poor outcome when proteinuria reaches levels exceeding 1 g per day at any time during the course of IgA nephropathy, but also the highly favorable prognosis of minimal proteinuria at onset. Only rarely did a patient with

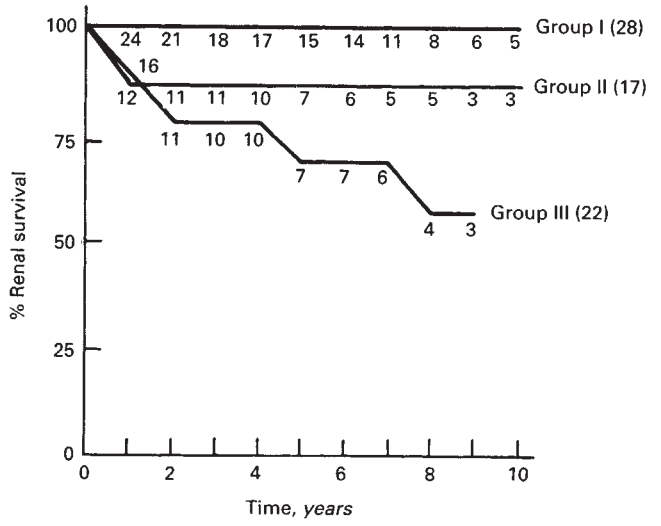

Fig. 3. *"Renal survival" (serum creatinine 2 mg/dl or less) in patients with different maximal levels of proteinuria during the course of IgA nephropathy.* Sixty-seven patients with serum creatinines not in excess of 2 mg/dl at presentation are the subjects of this analysis. "Survival" was significantly foreshortened in Group III as compared to Group I: $P < 0.001$. "Renal survival" 5 years after the first appearance of heavy proteinuria was 55% (not shown). The numbers of patients under observation each year are shown along the curves.

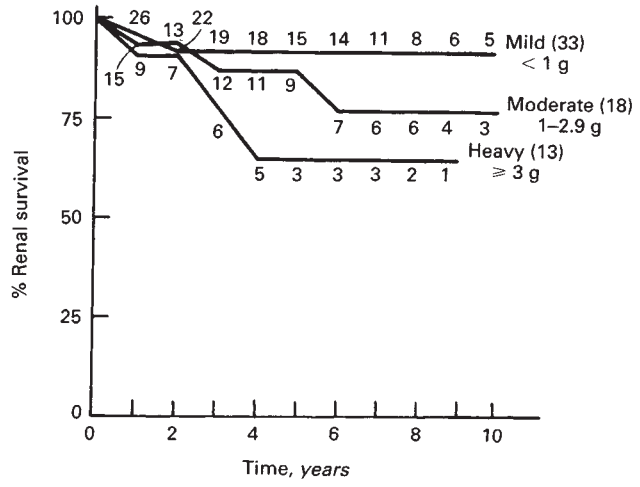

Fig. 4. *"Renal survival" (serum creatinine 2 mg/dl or less) according to level of proteinuria at the time of presentation with IgA nephropathy.* Sixty-four patients with serum creatinines not in excess of 2 mg/dl at presentation are the subjects of this analysis. Relataive risk of renal functional impairment (serum creatinine over 2 mg/dl): moderate vs. mild—2.5, heavy vs. mild—6.3. The numbers of patients under observation each year are shown along the curves.

minimal proteinuria at presentation convert to a greater level carrying the increased likelihood of ultimate renal failure.

Proteinuria and morphologic features. The percentage of patients with different morphologic features according to level of proteinuria at the time of renal biopsy is shown in Table 1. Mesangial proliferation was more frequent and more severe with moderate and heavy proteinuria, as were the incidences of segmental and global proliferation in glomeruli. Increasing percentages of patients manifested small crescents and circumferential crescents according to level of proteinuria, but these correlations did not reach statistical significance. An increase in disease-related glomerular sclerosis as previously defined by us [18, 19] was found in 24%, 53% and 59% of patients at the different levels of proteinuria (Chi-squared 2Df = 6.148, $P < 0.05$; mild vs. heavy $P < 0.05$).

On electron microscopic examination, only podocyte effacement bore a statistical correlation to level of proteinuria. It was present in 43% of those with mild, 94% of those with moderate and 92% of those with heavy proteinuria and was more severe in the latter two groups. No correlation existed between level of proteinuria and increase in mesangial matrix, nor was there a correlation between level of proteinuria and deposits in the mesangium, subendothelial, intramembranous or epimembranous regions, glomerular basement membrane abnormalities, or the prevalence of immunoglobulins M or G.

Interstitial infiltration and tubular atrophy were present in greater numbers of patients and with greater severity at the higher levels of proteinuria. Vascular sclerosis was of greater severity in those with greater proteinuria, although its incidence did not differ significantly among the different groups.

Five patients with persistent heavy proteinuria underwent biopsy prior to deterioration of renal function, when serum creatinine concentrations were less than 2 mg/dl. Upon follow up, four developed end stage failure and the fifth had a serum creatinine concentration of 2.1 mg/dl. The morphological features of these patients consisted of mesangial proliferation, segmental and global proliferation, partial and circumferential crescents, "significant" or disease related glomerulosclerosis, vascular sclerosis and tubulointerstitial changes. The findings in these patients support the view that heavy proteinuria may be a marker of advanced morphological damage even prior to clinically evident renal functional impairment.

Discussion

The present study demonstrates the prognostic significance of level of proteinuria in IgA nephropathy. Mild proteinuria at presentation predicted a favorable outcome, since fewer than one in eight later developed heavier proteinuria, and none who remained with minimal proteinuria (Group I) progressed to renal insufficiency. Forty percent of those who reached heavy levels of proteinuria (Group III) and 25% in whom the maximum excretion was moderate (Group II) developed increased serum creatinine concentrations, while this never occurred in any patient with mild proteinuria. One-sixth of those with more than minimal proteinuria progressed to end-stage renal failure. Compared to patients with mild proteinuria at onset, the relative risk of ultimately incurring renal functional impairment was 2.5 times greater in the group who started with moderate proteinuria and 6.3 times greater in those who had heavy proteinuria on presentation. Hypertension was observed as a concomitant of renal functional impairment in a significant number of patients but more importantly, the present data demonstrate that heavy proteinuria precedes the appearance of hypertension in the majority of cases. These findings in IgA nephropathy serve to underscore the significance of impaired permselectivity as an early and sensitive marker of glomerular injury.

Table 1. Level of proteinuria and morphological features

Proteinuria	Mild <1 g	Moderate 1 = 2.9 g	Heavy >3 g	*P* value	
No. of patients	27	21	20		
Mesangial proliferation					
Absent	26%	0%	0%	Mild vs. mod.	<0.05
Grade 1	11%	14%	5%	Mild vs. heavy	<0.01
Grade 2	63%	86%	95%	Overall	<0.01[a]
Segmental proliferation	18.5%	42.9%	55%	Mild vs. heavy	<0.05
Global proliferation	0%	4.8%	25%	Overall	<0.03[b]
Partial crescents	11%	28.6%	35%	Overall	<0.03[b]
Circumferential crescents	0%	4.8%	10%	NS	
Disease-related or "significant" glomerulosclerosis	24%	52.6%	58.8%	NS	<0.05
				Overall	<0.05[b]
Podocyte effacement					
Absent	56.5%	6.25%	7.7%	Mild vs. heavy	<0.001
Grade 1	43.5%	81.25%	76.9%	Mild vs. mod.	<0.001
Grade 2	0%	12.5%	15.4%	Mild vs. heavy	NS
				Mod. vs. heavy	<0.005[a]
				Overall	
Interstitial infiltraiton					
Absent	66.6%	42.9%	25%	Mild vs. mod.	<0.05
Grade 1	33.3%	38.1%	50%	Mild vs. heavy	<0.05
Grade 2	0%	19%	25%	Overall	<0.02[a]
Tubular atrophy					
Absent	70.4%	33.3%	20%	Mild vs. mod.	<0.003
Grade 1	29.6%	38.1%	45%	Mild vs. heavy	<0.001
Grade 2	0%	28.6%	35%	Overall	<0.005[a]
Vascular sclerosis					
Absent	63%	33.3%	50%	Mild vs. mod.	<0.01
Grade 1	11%	14.3%	0%	Mild vs. heavy	<0.05
Grade 2	26%	19%	5%	Overall	<0.03
Grade 3	0%	33.3%	45%		

Morphological features in IGA nephropathy classified according to level of proteinuria at the time of renal biopsy
[a] Kruskal-Wallis test for ordered classification
[b] Chi-Squared for 2Df

Other investigators have shown that heavier proteinuria carries a poor prognosis in this disease, based on outcome at the end of a follow up period without the use of life table analysis [6, 7, 10, 11, 13, 20, 21]. When life table analysis has been utilized, patients with fairly advanced renal insufficiency may have been included at the entry point [22]. Identification of heavier proteinuria as an early prognostic feature is not achieved in these studies. In this regard our study is comparable to those of Droz et al from France [23] and Chida, Tomura and Takeuchi from Japan [24], and emphasizes the predictive value of protein excretion rate early in IgA nephropathy.

When heavy proteinuria appeared during the course of IgA nephropathy, it proved to be persistent and carried with it a poor prognosis, as summarized above. However, in a small subset of patients who had an onset with heavy proteinuria associated with features similar to "acute nephritis," that is, with fluid retention and transient hypertension, a remission in proteinuria often occurred and they suffered no subsequent renal functional impairment. This form of presentation has also been reported by D'Amico et al [9] and by Clarkson et al [20].

Heavy proteinuria was common in the present study, occurring in one-third of patients. A similar prevalence has been observed by Croker, Dawson and Sanfilipo [12], although others have generally reported a less frequent occurrence, ranging from 4% to 18% [7, 9, 10, 13, 19]. This cannot be explained by any significant difference in selection of patients for biopsy, since the various modes of presentation were represented equally in these other series and in ours.

The appearance of heavy proteinuria many months or years after onset and its relative infrequency set IgA nephropathy apart from most other primary glomerular diseases in which the nephrotic syndrome occurs. Minimal change, membranous nephropathy and focal glomerular sclerosis display heavy proteinuria almost invariably and typically on presentation. The delayed appearance of nephrotic syndrome in IgA nephropathy resembles somewhat the course of membranoproliferative glomerulonephritis, in which heavy proteinuria, albeit more common, is often not manifested until years of disease have elapsed, and has a similarly poor prognosis. In a multivariate analysis of age, recurrent macroscopic hematuria, proteinuria and hypertension, D'Amico et al have shown proteinuria of greater than 1 g/day to be the only independent clinical feature associated with poor prognosis [22].

Not unexpectedly, an association between level of proteinuria and severity of morphological damage was observed, supporting the unfavorable prognostic import of greater protein loss. Both proliferative and sclerosing lesions correlated with level of proteinuria, as did tubulointerstitial damage and vascular sclerosis, and disease-related glomerulosclerosis was present in more patients with heavier proteinuria. A correlation between glomerulosclerosis and heavy proteinuria has been noted similarly by others [13, 19]. In examining the morpholog-

ical features of a subset of patients with normal renal function and heavy proteinuria who eventually developed functional loss, we noted severe structural damage. The findings in these patients demonstrate that heavy proteinuria is a highly sensitive marker of glomerular damage in IgA nephropathy.

Our study also indicates that older age at presentation carries a poor prognosis. However, in IgA nephropathy, which may be recognized only by casual discovery of abnormal urinalysis or by manifestations of advanced disease, precise time of onset is often unknown. Hence it is not possible to state with certainty whether the disease is necessarily more severe as it occurs in older patients or whether these individuals represent a selected group in whom ongoing disease has been present for a longer period prior to diagnosis.

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